

CLAIMS

1. A pharmaceutical composition for oral administration comprising:
 - (i) N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N- (2- quinolylcarbonyl) -L-asparaginyl]amine]butyl]-(4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir), or its pharmaceutical acceptable salts as the active ingredient;
 - 10 (ii) a long chain fatty acid of C₁₂₋₁₈,
 - (iii) at least an alcohol of chain C₂₋₄;
 - (iv) a non-ionic surfactant;
 - (v) a pharmaceutical acceptable antioxidant
- 15 2. Pharmaceutical composition in accordance with claim 1, characterized by comprising N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N- (2-quinolylcarbonyl) -L- asparaginyl]amine]butyl]-(4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir), or its pharmaceutical acceptable salts, in a
20 concentration ranging from 10% to 80% in weight of the final composition;
3. Pharmaceutical composition in accordance with claim 2, characterized by comprising N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N- (2-quinolylcarbonyl) -L- asparaginyl]amine]butyl]-
25 (4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir), or its pharmaceutical acceptable salts, in a concentration ranging from 15% to 70% in weight of the final composition;
- 30 4. Pharmaceutical composition of claim 1, characterized by comprising a fatty acid of C₁₂₋₁₈ in a concentration

ranging from 20% to 80% in weight of the final composition;

5. Pharmaceutical composition of claim 4, characterized by the fatty acid of C₁₂₋₁₈ is preferably oleic acid, used in a concentration ranging from 20% to 70% in weight if the final composition;
6. Pharmaceutical composition if claim 1, characterized by using an alcohol of C₂₋₄, being this alcohol preferably ethanol, or propyleneglicol and or mixtures between them, preferably in a concentration ranging from 2% to 20% in weight of the final composition;
7. Pharmaceutical composition of claim 1, characterized by comprising a non-ionic surfactant selected among polyethoxylated derivatives from castor oil and the polyoxyethylene sorbitan esters (polysorbates) in a concentration ranging from 0.1% to 30% in weight of the final composition;
8. Pharmaceutical composition of claim 7, characterized by comprising among polyethoxylated derivatives from castor oil preferably the polyethoxylated castor oil 35 (Cremophor EL) and or polyethoxylated hydrogenated castor oil 40 (Cremophor RH 40), in a concentration ranging from 0.1% to 30% in weight of the final composition;
9. Pharmaceutical composition of claim 7, characterized by comprising among the polyoxyethylene sorbitan esters preferably the liquid polysorbates like polissorbate 20, 40, 60 and 80, in a concentration ranging from 0.1% to 30% in weight of the final composition;

10. Pharmaceutical composition according to claim 1, characterized by comprising a pharmaceutical acceptable antioxidant selected from alpha-tocopherol and butylated hidroxytoluene, in a concentration ranging from 0.001 % to 2.0% in weight of the final composition;
11. Pharmaceutical composition according to claims 1 to 10, characterized by consisting of a stable concentrate microemulsion wherein the active ingredient N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N- (2- quinolylylcarbonyl) -L-asparaginylyl]amine]butyl]-(4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir), or its pharmaceutical acceptable salts, is soluble;
12. Pharmaceutical composition according to claim 11, characterized by being fractionated in single doses in the form of soft gelatin capsules or in the form of hard gelatin capsules for oral administration in the treatment of AIDS;
13. Pharmaceutical composition according to claim 12, characterized by being preferably fractionated in single doses in the form of soft gelatin capsules for oral administration in the treatment of AIDS;
14. Pharmaceutical composition according to claims 1 to 13 in wich the bioavailability of the active ingredient, when measured by AUC and C_{max} parameters, is at least 5 times higher than the same dosage from the reference composition.
15. A process for preparing a pharmaceutical composition which comprises the following steps:
- (a) Completely dissolving of N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N- (2-

- 5 quinolylcarbonyl) -L- asparaginy]amine]butyl]-
 (4aS,8aS)-isoquinolone-3(S)-carboxamide , or its
 pharmaceutical acceptable salt, in a sufficient
 amount of the alcohol of C₂₋₄ under controlled
 temperature;
- (b) Eliminating particles by filtration;
- (c) Adding the fatty acid of chain C₁₂₋₁₈, the
 antioxidant and the surfactant in an appropriate
 amount used in the composition;
- 10 (d) Evaporating the alcohol at a maximum temperature
 of 50°C under reduced pressure;
- (e) Optionally, adding the surfactant from step (c)
 after the evaporation of the alcohol from step
 (d);
- 15 (f) Adding the alcohol C₂₋₄ under stirring and in an
 enough amount to complete the adequate weight of
 the final composition
16. Process according with claim 15, characterized by
 comprising in step (a) the compound N-tert-
20 butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N-
 (2- quinolylcarbonyl) -L- asparaginy]amine]butyl]-
 (4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir),
 or its pharmaceutical acceptable salts, in the
 crystalline, amorphous, micronized or mixtures of
25 that forms, in a concentration ranging from 0.01% to
 90% in weight of the final solution;
17. Process according with claim 15, characterized by
 comprising an alcohol of chain C₂₋₄ in step (a) is
 used in a concentration ranging from 10% to 99.99% in
30 weight of the final solution;
18. Process according to claim 17, characterized by the
 alcohol of chain C₂₋₄ used is the ethanol;

19. Process according with claim 15, characterized by using in step (a) temperatures ranging from 20°C to 50°C;
20. Process according to claim 15, characterized by the fatty acid of chain C₁₂₋₁₈ used in step (c) is the oleic acid;
21. Process according to claim 15, characterized by the antioxidant used in step (c) is the tocopherol, or the butylated hydroxytoluene or mixtures between them;
22. Process according to claim 15, characterized by the non-ionic surfactant used in step (c) or (e) is the polyethoxylated castor oil 35 (Cremophor EL) or the polyethoxylated hydrogenated castor oil 40 (Cremophor RH 40);
23. Process according to claim 15, characterized by using in steps (c) or (e) the polyoxyethylene sorbitan esters, preferably the liquid polysorbates as polyssorbate 20, 40, 60 and 80;
24. Process according to claim 15, characterized by in step (d) the maximum temperature used for the evaporation of the alcohol of chain C₂₋₄ is 50°C;
25. Process according to claim 15, characterized by the alcohol of chain C₂₋₄ used in step (f) is the ethanol, or propyleneglycol, or mixtures between them;
26. Process according to claim 15, characterized by the resulting product presents N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N- (2-quinolyl)carbonyl] -L- asparaginy]amine]butyl]-(4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir) or its pharmaceutical acceptable salts, in a

concentration ranging from 10% to 80% in weight of the final pharmaceutical composition;

27. Process according to claim 26, characterized by the resulting product contains the compound N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N-(2-quinolylcarbonyl) -L- asparaginy]amine]butyl]-(4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir), or its pharmaceutical acceptable salts in a concentration preferably ranging from 15% to 70% in weight of the final pharmaceutical composition;
28. Process according to claim 15, characterized by the resulting product contains the fatty acid of chain C₁₂₋₁₈ in a concentration ranging from 20% to 80% in weight of the final pharmaceutical composition;
29. Process according to claim 28, characterized by the resulting product contains the oleic acid as the fatty acid of chain C₁₂₋₁₈, in a concentration ranging preferably from 20% to 70% in weight of the final pharmaceutical composition;
30. Process according to claim 15, characterized by the resulting product contains the ethanol, or propyleneglycol or mixtures of them as the alcohol of chain C₂₋₄, in a concentration ranging from 2.0% to 20% in weight of the final pharmaceutical composition;
31. Process according to claim 15, characterized by the resulting product contains as the non-ionic surfactant the poliethoxylated ethers of castor oil, or the polyoxyethylene sorbitan esters (polysorbates), in a concentration ranging from 0.1% to 30% in weight of the final pharmaceutical composition;

32. Process according to claim 31, characterized by the resulting product contains preferably the polyethoxylated castor oil 35 (Cremophor 35) and/or poethoxylated hydrogenated castor oil 40 (Cremophor RH 40) as the non-ionic surfactant the polyethoxylated derivatives of castor oil, in a concentration ranging from 0.1% to 30% in weight of the final pharmaceutical composition;
33. Process according to claim 31, characterized by the resulting product contains as the non-ionic surfactant, the polyoxyethylene sorbitan esters (polysorbates), the liquid polysorbates like polyssorbate 20, 40, 60 or 80, in a concentration ranging from 0.1% to 20% in weight in the final pharmaceutical composition;
34. Process according to claim 15, characterized by the resulting product contains the alpha-tocopherol or the butylated hydroxytoluene as the antioxidant, in a concentration ranging from 0.001% to 2.0% in weight of the final pharmaceutical composition;
35. Process according to claim 15, characterized by furnishing a stable concentrate microemulsion wherein the active ingredient is soluble, and which is suitable for being encapsulated in hard or soft gelatin capsules for the oral administration in AIDS treatment.
36. A method to increase bioavailability of N-tert-butyldecahydro-2-[2(R)hydroxy - 4-phenyl-3-(S)-[[N-(2- quinolylcarbonyl) -L- asparaginy]amine]butyl]-(4aS,8aS)-isoquinolone-3(S)-carboxamide (saquinavir), or its pharmaceutical acceptable salts, which consists in administering to a patient during the

therapy a pharmaceutical composition prepared
according to claims 15 to 36.